Report of The Scientific Review Group

Joint Coordinating Committee For Radiation Effects Research

June 19th, 1996

Washington, D.C.

Overview:

The Scientific Review Group (SRG) met on June 19, 1996, to review Proposals submitted in relation to Directions 1 and 2. The participants of this meeting are listed in an addendum. The proposals under review included proposals 1.1, 1.2, and 2.1. These proposals were reviewed individually by the committee. In reviewing the proposals, the SRG was uniformly concerned about issues of coordination and communication that impinged on the quality of the scientific proposals. Consequently, although the principal task of the SRG is scientific peer-review, the group considered it necessary to identify and address issues related to overall scientific management. These issues require urgent resolution if the scientific promise of the activities taking place under the Joint Coordinating Committee for Radiation Effects Research (JCCRER) is to be fulfilled. This report of the SRG thus provides both peer review for the individual proposals and more general comments concerning the research program.

General Comments:

The SRG remains convinced that research on the Mayak workers and the general population in the Urals could provide a substantive scientific contribution in addressing current issues related to the health risks of radiation exposure. A key objective of the research that can seemingly be fulfilled would be the development of risk estimates for cancers associated with protracted external radiation and internal emitters. The population patterns of exposure and the quality of the data available indicate the potential to obtain informative risk estimates. There is also an opportunity to learn more about the non-stochastic effects of internal emitters by studying the more highly exposed workers. New insights concerning dosimetry could also be gained by analysis of existing materials and by further studies using biomarkers. Carefully integrated research, employing state-of-art dosimetric and epidemiologic methods, will be needed. An essential first step is characterizing the sources of radiation exposure as a basis for planning the dose reconstruction. Valid dose reconstruction is a key element of this program.

The promise of this research will only be met if there is a long term commitment to funding at an appropriate level and to assuring that proper technical and administrative support are provided. The funding agencies need to recognize the commitment that is required, both in regard to amount and duration of funding.

Review of the proposals made clear that the present administrative arrangements are not working satisfactorily. The SRG identified a series of issues that need to be addressed: 1) lack of an overall scientific management plan for the projects, designed to smoothly lead to accomplishment of the scientific objectives; 2) seemingly inadequate coordination among the investigative groups working on the individual projects, for example, with an artificial distinction between the teams addressing dosimetric and epidemiologic issues; 3) a failure of coordination between research being funded by the JCCRER and that being conducted by the National Cancer Institute and other agencies; and 4) a failure to set clear priorities for the designated goals. While resolution of these issues does not lie within the scope of the SRG's formal mandate, we request that they be addressed on an immediate basis by the JCCRER and its Executive Committee. An overall plan is needed that integrates the tasks that now lie

within the individual proposals. The current fragmentation should be replaced by a coordinated research program that fully integrates the currently separated activities related to dosimetry and epidemiology; these activities need to proceed with coordination and extensive interaction between the investigators. A new management approach is needed to achieve this end. Furthermore, the parallel activities of the National Cancer Institute must be an integral part of this research program. The parent agencies need to work together closely because of the complementarily of the projects funded by the JCCRER and the National Cancer Institute.

The SRG considered that the scientific quality of the proposals had been affected by these programmatic issues. Nevertheless, it carried out its scientific review and also considered the priority that might be given to the various research projects. Proposal 2.1 was considered meritious and likely to provide informative results with its proposed work scope and budget. The proposed work is essential to estimating doses for workers and characterizing the uncertainty of dose estimates; there is also the potential to immediately learn a great deal about dosimetry of internal emitters and to assess the validity of widely used dosimetric models. The SRG also supported the archiving of hard copy materials, as proposed in Proposal 1.2a, although it identified technical limitations of the proposal that need to be addressed and are specified in the detailed comments. The SRG was generally supportive of the work in progress under Proposal 2.3, which addresses non-stochastic effects in a unique, more highly exposed population of workers. The data being acquired are as appropriate as current knowledge, technology and logistics will permit, and are within reasonable limits for a data gathering exercise. However, thought should be given sooner, rather than later, to archiving serum, cells and tissues (e.g., blood cells and tissue biopsies) for studies at a later date, when more sensitive tests for radiation injury become available, for example molecular studies such as detection of specific gene alteration. The potential for molecular epidemiological studies in this field is increasing. Therefore, some guidelines regarding the prioritization and authority to allocate archived materials to scientists in future studies should be established. In addition, arrangements for materials storage, ideally in multiple aliquots, should be made.

With regard to Direction 1, the SRG was not supportive of implementing Proposals 1.1 and 1.2b in their present form. Proposal 1.1 was still regarded as too sweeping; accomplishing the proposed work will require substantially more time and funds than were proposed. Emphasis should be placed on characterizing the source terms for radiation exposure and then moving on to considering population dosimetry. Proposal 1.2b, while proposing work that needs to be done, lacked specificity and concern was expressed about the details of how the work would be accomplished. Above all, there was a lack of coordination and integration between the proposals for 1.1 and 1.2b that diminished enthusiasm.

The SRG considered approaches to addressing perceived deficiencies of the work proposed under 1.1 and 1.2b. The group considered that specific issues could not be readily resolved until an overall plan for approaching the health effects of exposure to the general population was developed. Coordination among the two investigative groups and the investigators of the National Cancer Institute was regarded as essential, given the overlapping nature of the

epidemiologic studies. The SRG suggests that a meeting with the investigators and the SRG members would be helpful, both as a basis for answering questions not covered in the proposals and for having a supportive exchange. A meeting should be scheduled, ideally involving the Russian investigators, but only after a comprehensive management and technical plan has been developed.

Finally, the SRG urges the JCCRER to consider the range of approaches that might prove successful for accomplishing a large scale and long term program of research in the Urals. There are a number of models to be considered, e.g., RERF or appointing full-time investigators from the U.S. and Russia to coordinate activates. While not so urgent as the other management issues discussed above, the SRG would encourage the development of a long-range plan for establishing and maintaining a binational research program of substantial magnitude and long duration.

The SRG recognizes that funding is currently limited and that the budgets of the submitted proposals exceed the total amount now available. It suggests that priority be given to the studies of workers as funding decisions are made, particularly to Project 2.1 and to completing the present Project 2.3. While the SRG was not supportive of the proposals for 1.1 and 1.2b as submitted, it suggests that sufficient funding be provided to assure that the Russian investigators can continue to develop data bases and to maintain communications with their U.S. counterparts, while a more complete plan is assembled. Sufficient support should be provided to the U.S. and Russian investigators for the purpose of developing this plan.

Participants:

This meeting was attended by Dr. Jonathan Samet (chair), Drs. Marvin Goldman, Geoffrey Howe, David Rush, John Till and Rodney Withers. Dr. John Poston submitted his written comments, as he was unable to attend this meeting in person, and reviewed the draft of the General Comments. The observers from the Department of Energy at this meeting were Dr. Nga Tran, Dr. Mohandas Bhat, Mr. Frank Hawkins, Ms. Elizabeth White, Ms. Cherie Gianino, and Dr. Ruth Neta.

PROPOSAL 1.1 (Score 2.5)

This objectives of this project are crucial to the overall goals of estimating risk to populations exposed to radionuclides released from the Chelyabinsk region. Therefore, the research itself is of high importance and must ultimately be carried out. The project as described applies the fundamental knowledge of dose reconstruction and takes advantage of experience in the U.S. and other countries where detailed dose reconstructions have been carried out.

The project, as presented, continues to be far too broad in scope and not well defined, especially in view of the budget proposed and the resources available. If this work is to be undertaken, significantly greater resources will need to be committed for a number of years. There is no clear separation of those tasks which, though labor intensive, are technological in nature, e.g., record extraction and summarization, fitting data to models from the science, e.g., development of new models, development of sensitive bio markers, etc. A grand scheme of priority and time, a matrix of sorts, would help clarify the priorities and levels and durations of effort, e.g., a Gannt or PERT chart.

A serious shortcoming of the research is the lack of emphasis given to an early detailed characterization of the source term, enabling defensible dose estimates to be made. There is some question on the part of the SRG whether a detailed source term can be derived and to what extent validation data are available.

Issues related to access to historical records, declassification of documents, and access to facilities need to be resolved. It appears that some of the data on early releases that is vital to the success of the reconstruction events, is still classified. Progress is being made on this sensitive topic. The question now is whether there are any impediments to ultimately getting the needed data? The issue is not trust amongst the investigators, but of free access to the primary data sources by the Russian investigators. Who is on top of this and are the necessary safeguards in place so that security issues will not become a stumbling block? Since most of the significant radiological data are from before 1960, is there any political obstacle in sight? Is the inventory of data complete; that is, do we know what all the data sources are, and which may still need declassification action?

A key question with regard to the Techa River Cohort is to what extent the cohort may have been exposed to radionuclides from other pathways, e.g., inhalation, that may lead to an underestimation of the total accumulated dose. Without careful development of the source term and its uncertainties, estimates of risk will be highly suspect. Therefore, the SRG believes characterization of the quantities and types of radionuclides released, both routine and accidental, in the Chelyabinsk region should be given the highest priority.

Principal scientists on the proposal are certainly well qualified and have the broad range of skills needed for this unique dose reconstruction. However, it is not described in the proposal who would actually be carrying out the day-to-day work that would need to be done. Certainly the leading scientists would not appear to have the time required to do such a labor intensive effort as it is proposed. For example, there are listed in the proposal 36 "final

reports" that are to be developed and submitted during the course of the study. These do not include numerous intermediate steps that are also listed to be completed.

The tasks to determine individual doses by whole-body counting, cellular markers and tooth enamel EPR are laudatory, but should be independent of the overall population dose reconstruction effort coupled tightly to the epidemiological work. Their major promise is as a set of tools for quality control, model validation and uncertainty reduction, especially since most of the doses are non-uniform in the body in space and in time. Although the biodosimetry effort ideally should proceed parallel to the main dosimetry, funds may not be available to invest significantly at this time. There is a real justification to strenuously seek co-sponsorship to develop in-house expertise.

There is a strong desire to develop in-house biological dosimetric expertise, but it should not proceed at the expense of the overall dose reconstruction efforts. However, initially, independent, blind, off-site sample measurements may provide a good start.

The budget proposed significantly underestimates the work that has been proposed. The cost of up-grading the whole body counter seems inflated, although improvements are needed.

Project 1.2A (Score 2.5)

1. Importance to the Rest of the Program:

   The preservation of the basic data is absolutely critical to the success of any future studies.

2. Merit of Scientific Hypothesis:

   Not applicable.

3. Likelihood of Success:

   Data storage can be considered in two parts, namely, the physical preservation of existing records, and the creation of an electronic data management system. The former issue is not directly addressed in the report, but there seems no reason why it could not be readily achieved. The feasibility of the latter objective cannot be assessed at this stage because of inadequate information in the report as discussed below.

4. Appropriateness of Methods:

   The report focusses on the creation of an electronic data management system both for existing records and any records which will be updated in the future. This clearly is a highly desirable objective, but the present report is inadequate to make a judgment on its feasibility. The main points which need to be answered are.

   A) The proposal depends essentially entirely on scanning procedures to read all the relevant documents. There is no mention of what proportion of these documents are hand written, which, in general, makes it impossible for the scanners to handle. Further, no mention is made of quality assurance. Even for printed or typewritten documents, scanning is by no means perfect, and there is no discussion of how error rates will be determined, or what would be an acceptable error rate.

   B) No real prioritization has been specified for processing the various documents, nor is there any real consideration of what types of records will really be useful in future studies. Given the large number of documents, some sort of prioritization is essential for the process to be cost-effective.

   C) No description is provided as to which specific software and hardware will be utilized.

   D) No details are provided on training arrangements; we note the total budget for training is $5000 in the first year which seems completely inadequate.

   E) No mention is made of any quality assurance procedures, in addition to those raised above regarding scanning.

F) No consideration appears to have been given to the physical security of the existing documents, e.g., provision of storage facilities which are fire proof, damp proof, etc. These may already exist but will be helpful if this could be clarified.

5. Investigators:

It is not clear that the necessary expertise and experience exists on site to set up a complex electronic data management system. It is also unclear that the appropriate expertise is provided by the current American team.

6. Budget:

A) No specific details are provided for the Russian budget. For example, although total salary costs are provided, no information is given as to how many individuals will be funded from the budget. A very large part of the Russian budget goes to overheads and taxes. This may well be justifiable, but leaves a relatively small amount to cover what is likely to be a very complex undertaking and it is by no means obvious that this remaining budget will be adequate for the purpose. Though amounts are quoted for hardware and software, again no specific details are provided.

B) No American budget is currently available at this point.

7. Summary and Rating:

Overall, the objective of this proposal is laudable, i.e., to create an effective electronic data management system. However, the current proposal lacks sufficient detail to be able to evaluate the likely success of the project. In particular, our concerns are over the adequacy of the budget, and lack of consideration given to specifics of the computer software, computer hardware, quality assurance and training. Our overall rating is 2.5, which reflects the critical importance of this project to the rest of the studies, but at the same time our concerns over the adequacy of the present version of the proposal.

Project 1.2B (Score 2.75)

1. Importance to the Rest of the Program:

   This is a key study to the overall success of the program; nonetheless, other projects in the current program do not depend upon the successful completion of this particular project. It is, however, diffuse with many large tasks described briefly in a sentence or two.

2. Merit of Scientific Hypothesis:

   This study could provide important data on the risks of cancer and possibly other diseases following long term chronic exposure to high doses of ionizing radiation.

3. Likelihood of Success:

   There are several reasons why the project may not achieve its stated objectives. There is uncertainty in individual dose estimates, from possible biases arising from for example, loss to follow-up, and from uncertainties of completeness and accuracy of ascertainment of outcome. There is some attention to validation in the proposal, but details are minimal. In addition, all the authors' attention is addressed to the validation of pathologic diagnoses (with tissue inspection, or by supplemental interrogation of families, or scrutiny of medical records, etc). On the other hand, one of the realities of this study, which is not mentioned in the proposal, is that the cancer rates which have been reported heretofore are considerably lower than those expected from other key studies of the relationship of radiation to cancer. One possible explanation is under- or misdiagnosis. The ultimate credibility of these studies from the Chelyabinsk area therefore depends as much on the validation of negative as of positive diagnosis. This was stressed in the 1995 workshops in Florida and in Russia. There is nothing in the proposal that describes any activity to validate negative diagnoses.

4. Appropriateness of Methods:

   The methods proposed for improving the quality and quantity of the follow-up data are poorly specified. One aspect of the study which needs further justification is the desire to identify a "control" population. The issue of a comparison population is never adequately dealt with, and may be ultimately illusory, given the possibility of unrepresentativeness because of non-radioactive carcinogenic exposure, of almost any potential control population drawn from the former Soviet Union. The ultimate analysis will almost surely depend far more on gradations of outcome by dose, rather than comparison with some differentially evaluated reference population. (It is also unlikely we can ever feel confident that any geographically specified reference population received the same level of diagnostic scrutiny as the exposed cohorts). Calculating observed and expected values for the two cohorts is probably of little general interest since differences could well arise because of different underlying cancer rates in the exposed and comparison populations. Incorporating external rates into a dose response relationship would add a little power, but

again is subject to the potential problem of non-comparability.

The plans for statistical analysis are not well developed at this stage; however, given the amount of work to be done in the first three years on follow-up and verification of data it seems unlikely that any detailed or definitive analyses could be conducted in that time frame.

It is essential that the present program work in collaboration with the currently ongoing NCI funded project, and that there be no duplication of effort. The interrelationship between the work of this project and that of the National Cancer Institute, responsible for the epidemiology on the Techa River cohort through 1992, therefore, needs to be explained in detail. There appears to be much redundancy, and possibly work on the Techa River cohort should be deferred until this is clarified.

5. Investigators:

Since the last time that we met, the project staff has been changed. Dr. Ron no longer appears as the central American collaborator, except for the NCI project which carries the Techa River cohort through 1992. The Committee is uncertain that the new team has the necessary background and experience in large scale radiation epidemiology studies to successfully complete this ambitious project.

6. Budget:

The Russian budget appears to be reasonable and justified.

7. Suggestions for Clarifications and Modifications:

There is an urgent need for a spreadsheet so that the relationship between the data described on page 33 (the URCRM archive) and those on pages 46 and 47 (status of the main registries and amount of information in database other files) can be rectified. We need to see the cross-classification of availability of records.

It is also essential that there be a hierarchy of priorities, specifying steps essential for getting basic work completed, with a detailed description of the amount of effort each step requires to reach successful conclusion.

8. Project Goals:

A worthy goal for the first year of study would be to present a fully computerized relational data base, cross-referenced so that availability of specific information for each individual in the cohorts is known, as well as a beginning of substudies on data quality, and concrete information on worthwhileness of attempting to add new data elements to the research archive. The validation of death certificate diagnosis is a key issue as is the

relationship of morbidity to mortality information. Another central issue is the possibility that the 30% of unretrieved death certificates (page 11) are not random, but rather might in some way be systematically biased. This would occur, for instance, if those who ultimately died had moved to other regions because of their illness, i.e., in order to receive care or be with family. While probably considerably less likely than for the Mayak industrial cohort, it also applies to these populations.

9. Summary and Overall Rating:

This potentially is an important epidemiologic study with a uncertain likelihood of success. Initial funding should be for one year only, with continued funding dependent on the results of the progress report to be submitted at the end of the first year.

PROJECT 2.1 (Score 1.5)

This activity has a number of specific goals and objectives which are designed to link more effectively the Dosimetry Registry of the Mayak Industrial Association (DRMIA) and the United States Transuranium and Uranium Registries (USTUR). The two human tissue research programs have similar objectives: to ensure the adequacy of radiation protection standards for actinide elements and verifying or modifying, as appropriate, the existing biokinetic and dosimetric models on which standards for the actinide elements are based. Both programs have been in existence for approximately the same length of time and each has a collection of dosimetric, medical and autopsy tissue radiochemical analytical data for occupationally-exposed workers from plutonium facilities in the respective countries. The similarities and differences of these two programs were explored as a first phase of this activity.

The SRG believes that this work is of high importance and with a few modifications should be fully supported. These modifications will make the research more meaningful and enhance its chances for making a significant contribution to science. Incorporating dedicated expertise in statistics/biostatistics would permit the researchers to better evaluate the distribution of radionuclides within organs of the body. This information could then be used to help quantify uncertainties that could be applied to the internal dosimetry and pharmacokinetic models.

Addend these facets to the research scope will add greatly to the project's potential benefit.

The current report (USTUR-0053-96) presents a number of specific objectives (tasks) with estimated completion dates spaced over the next several years. No budgets or estimates of time and effort of the investigators is presented. Therefore, the review concentrates solely of the short discussions of the tasks. These tasks are listed below and short discussions are provided as necessary.

Task A: Compare radiochemical analytical methods for actinides currently in use by both Programs with a series of performance evaluations. Intercomparisons of the methods and equipment is necessary to assure the compatibility of existing data and to evaluate any consistent differences in analytical results. An initial exchange of acid-dissolved tissue samples will be used for this purpose. This task is necessary and appropriate and the completion date given seems reasonable.

Task B: Establish a common data base format that can be used by both Programs for completion of the other tasks listed in the proposal. This task is of primary importance to the success of the entire activity. As indicated, it has an early completion date which is necessary to ensure the success of the remainder of the activities.

Task C: Coordinate tissue sampling methods used in the two Programs including specific tissues and organs sampled, mass of the sample, and specific structures to be included in a sample, thus improving and making more exact data comparisons. This is one of the first

tasks to be completed (July 1, 1996) and the purpose if to bring some uniformity to the types of samples collected in the two Programs. Currently, there is a difference in the types of bone samples collected. A determination should be made as to whether this difference has a significant impact on dose reconstruction. This is a reasonable and important task and it is appropriate that it be one of the first scheduled for completion.

Task D: Coordinate radiochemical analytical methods used in the Programs to determine actinide contents of tissue samples, including ashing methods, actinide separation techniques, spectroscopy methods, and data recording. This important task will ensure the quality of the data obtained by bringing the latest technology to bear on the analysis of samples. The sensitivity of the analytical methods for tissue sensitivity for actinide assays, and for bioassay is another issue. The technique used by the FIB-1 team can be improved by a factor of 3 to 10, and this will be important for future measurements. The plans to cross-calibrate between the US and Russian labs is commendable and a long range plan for continued quality control, including split sample sharing is desired. The completion date seems reasonable considering the time and effort required.

Task E: Characterize work place aerosols in the Mayak facility and American facilities. Although this task may be important for future cases and could contribute to better general understanding of the aerosols, it is not apparent to this reviewer that there is a significant, anticipated return from this activity. In the U.S., most facilities that were operating when USTUR cases were exposed are essentially shutdown. I suspect the same is true at the Mayak facility. Since there is no indication of the effort to be devoted to this task nor the cost of such a task, it is not possible to make a judgment of time, effort, and cost versus scientific return. It would be helpful to have more discussion of this task and a better justification of the importance of the task to the success of the overall project.

Task F: Establish transfer coefficients that describe the transfer of various plutonium and americium compounds from the lungs to the blood and compare the coefficients with those predicted by the new ICRP respiratory system models. This is a reasonable task for the Programs and it is very important for the dosimetry of inhaled radionuclides - not just for plutonium and americium compounds. Even though this task focuses on the new ICRP models, in my opinion, this has been one of the primary goals of the USTUR since its inception. Please see recommendation under Task H.

Task G: Determine relationships between actinide concentrations of organs of the body and between individual organ contents and total body burdens in healthy individuals as well as those with health impairment, specifically those with liver diseases. This seems to be a very important task and the completion time seems to be appropriate. This has been one of the primary goals of the USTUR since its inception. Please see recommendation under Task H.

Task H: Test relationships between actinide contents of the lungs and body organs at autopsy and the long-term, temporal pattern of urinary excretion predicted by the current ICRP

metabolic models for plutonium and americium. Compare actinide metabolism and long-term excretion of the actinides in healthy individuals with that in health-impaired individuals, specifically those with liver disease. Although it may be the desire of the investigators to separate these tasks to "highlight" each, it appears that Tasks F, G, and H should be condensed into a single task, since these three tasks have very similar goals and need close coordination to be successful. Some thought needs to be given to the suggested completion dates for these three tasks. It is not immediately clear that the completion sequence is correct.

Task I: Enhance the sensitivity of the in vivo counter used by the DRMIA and perform calibrations and intercomparisons with other, similar facilities so that it is a more useful tool for characterizing the intake and retention of actinide elements.

While there is not disagreement that this is an important task, it is not clear why an "old technology" is being suggested as an "upgrade" of the DRMIA facility. The use of phoswich detectors is very old technology (at least 20 years old) and there are other more acceptable upgrades, in terms of defining radiation detectors for use in this application. There are no cost data presented for this "upgrade" but it does not make much sense to approve the expenditure of any funds to purchase equipment which has well-known limitations. In addition, no completion date is given for this task.

Task J: Translate previously classified Russian documents into English for submission to peer-reviewed journals for the publication as topical reports as appropriate. A worthy goal for this collaboration, but how many papers are anticipated and what is the anticipated completion date for this task?

Overall Evaluation: It is the opinion of the Scientific Review Group that the tasks proposed herein are appropriate for such a collaboration and we strongly recommend that the efforts be considered for continuation. We would assign a numerical rating of 1.5-2.0 to this activity. As pointed out above, some of the tasks have generated questions which need to be addressed.

No budget or listing of individual efforts was provided, so the review has been made without benefit of the anticipated effort or cost. However, it is our impression that the number of individuals involved and the costs are not large.

We recommend the addition of a statistician with an expertise of study design to the team. Throughout the proposal there was a lack of formal consideration of issues related to the selection of sampling of materials, estimation of sample sizes, and data analysis.